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Silent coronary heart disease in patients with type 2 diabetes: application of a screening approach in a follow-up study

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ABSTRACT

Aims: The cost-effectiveness of screening for silent coronary heart disease (CHD) in type 2 diabetes (DM2) is still debated.
Methods: We applied a diagnostic algorithm for silent CHD detection, in a cohort of 102 asymptomatic DM2 subjects (57 ± 7 years), attending 5 Italian outpatient clinics, to verify its predictive value. The risk of silent CHD was calculated considering classical risk factors, and presence of microangiopathy/macroangiopathy. Patients were divided in 3 groups, i.e. group 1: normal ECG and low silent CHD risk; group 2: abnormal ECG, irrespective of silent CHD risk; group 3: high silent CHD risk, irrespective of ECG. To group 2 and 3, a functional test was recommended and performed in 78% of patients.
Results: Silent CHD prevalence was similar in group 2 and 3 (25 vs. 17% respectively; p = 0.495). However, evaluating the entire cohort, a significant higher prevalence of silent CHD was observed in subjects with abnormal vs. normal ECG (23 vs. 4%; P = 0.004), but not in subjects with high vs. low pre-test silent CHD risk (14 vs. 9%; p = 0.472).
Conclusions: An abnormal ECG was a strong, independent predictor of silent CHD (OR 8.9; CI 1.27–62.5; p = 0.028) in DM2. Therefore, a functional stress testing should be considered in DM2 patients with ECG abnormalities.

1. Introduction

Patients with type 2 diabetes mainly die from ischemic heart disease or ischemic stroke, so their life expectancy is reduced by at least 6 years compared to the non-diabetic counterpart.[1] Any phenotype of heart disease significantly associate with diabetes, as recently confirmed in a wide population study, by Shah et al.[2] It is also well documented that coronary heart disease (CHD) in diabetes is more severe,[3] and more frequent than in non-diabetic subjects: about 75% of diabetic patients without a diagnosis of CHD show high-grade atherosclerotic coronary lesions, at post-mortem examination.[4] The prevalence of asymptomatic CHD in this population is round 20%, in most studies,[5–9] a figure higher than the non-diabetic individuals; therefore in type 2 diabetes the presence of silent myocardial ischemia is highly probable. Asymptomatic myocardial ischemia predicts cardiovascular events in this population, beyond the routine risk prediction.[10] For this reason, the cost-effectiveness of a screening strategy to detect silent CHD has been proposed although there is no unanimous consensus. Several guidelines have addressed this issue,[11–15] yet recommendations are often conflicting,[16] and a definite proof that screening programs to prevent cardiac events in patients with type 2 diabetes are worthwhile cost-effective is lacking. For this reason the Italian Societies for the Study of Diabetes (Società Italiana di Diabetologia, SID and Associazione Medici Diabetologi, AMD), and several Italian Societies of Cardiology and Atherosclerosis (Associazione Nazionale Medici Cardiologi Ospedalieri, ANMCO, Associazioni Ragionali Cardiologi Ambulatoriali, ARCA, Società Italiana di Cardiologia, SIC, Società Italiana per lo Studio dell'Aterosclerosi, SISA) have jointly addressed this topic, by proposing a flow-chart with the definition of the high risk of silent CHD, along with an instrumental diagnostic approach to detect silent CHD, in asymptomatic diabetic patients.[17]

The main aim of this study was to identify major predictors of silent coronary artery disease in T2DM patients with a very high pre-test risk of silent CHD; other aims were: 1. to verify the adhesion to this proposed

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screening protocol to detect silent myocardial ischemia in five outpatient clinics; and 2. to evaluate, in subjects screened for silent CHD, the cardiovascular outcomes at 12 and 30 months of follow-up.

2. Subjects

Five Italian Diabetes Centers participated in this study, and a total of 102 patients were enrolled. Participating centers were: the out-patient Diabetes Clinics of Cagliari University, Napoli Federico II University, Padova University, Pisa University, and S. Giovanni Rotondo (Foggia) Hospital. Recruitment and baseline clinical evaluations were performed from January 2012 to December 2012. Consecutive patients attending the above-mentioned outpatient clinics, who met the inclusion/exclusion criteria, were enrolled. Inclusion criteria were: age 35–65 years; type 2 diabetes diagnosed by ADA criteria since at least 1 year; absence of typical cardiac symptoms (chest discomfort, dyspnea, angina, etc.), and negative clinical history for cardiac disease; a recent (within 1 month) electrocardiogram (ECG); definition of the risk of silent myocardial ischemia on the basis of the Consensus suggested criteria (Fig. 1); willingness to participate in the study, and to attend periodical follow-up visits in the respective centers; signed informed consent. Exclusion criteria were type 1 diabetes; other major organ diseases or advanced chronic diabetes complications (i.e. chronic kidney disease stage ≥3; severe proliferative retinopathy; peripheral arterial disease Lériche-Fontaine stage ≥3), unwilling to participate. The study was approved by the local Institution and Ethical Committee of the University Hospital of Padova, and the approval was extended to all other centers.

3. Materials and methods

At baseline visit, clinical history, ongoing therapy, chronic diabetic complications, and blood pressure measurements were recorded in each subject. Main anthropometric (weight, height, BMI, waist circumference), and blood pressure measurements in sitting position were obtained after an overnight fasting, and a blood sample was collected to measure clinical chemistry parameters (glucose, glycated hemoglobin, total cholesterol, HDL cholesterol, triglycerides, AST, ALT, creatinine) by standard methods, in each center. LDL-cholesterol (Friedewald formula) and CKD-EPI GFR were also calculated. A urine spot sample was obtained to measure urinary albumin excretion (as albumin/creatinine ratio).

The enrolled subjects were then subdivided in the 3 following groups (Fig. 2): group 1, patients with a normal ECG report, but without a high probability of silent CHD. An ECG was considered "normal" even with an incomplete right bundle branch block, or with isolated 1st degree atrioventricular block; all other ECG interpretations were considered as "abnormal"; group 2, patients with an abnormal ECG, without a high probability of silent CHD; group 3, patients with high silent CHD risk, independent from ECG abnormalities. Patients included in groups 2 and 3 were then suggested to undergo a functional cardiac diagnostic test, in accordance with the Consensus algorithm (Fig. 2), taking into account patient's preference/contraindications. An ECG was repeated to patients allocated in group 1, as suggested, before the follow-up visit. Ongoing pharmacological therapy was possibly modified, during functional cardiac tests, in accordance with the good clinical practice recommendations.

A first follow-up visit was programmed after 12 months. During this visit, the diabetologist had: 1. to verify whether the suggested diagnostic algorithm was fulfilled; 2. to register the diagnostic test results; and 3. to collect the main cardiovascular clinical outcomes (acute myocardial infarction, AMI, transient ischemic attack, TIA, stroke, hospitalization for heart failure, peripheral by-pass or amputation). The anthropometric and biochemical parameters were repeated as outlined in baseline (Fig. 2).

A second follow-up visit was programmed after 36 months, for anthropometric and biochemical parameters, and cardiovascular events collection. Vital status and main cardiovascular event (MACE) occurrence were also investigated afterwards.

All the visits and diagnostic tests were performed in an outpatient regimen.

3.1. Statistical analysis

Continuous variables are expressed as mean ± SD, if normally distributed or median (interquartile range), if non-normally distributed, and categorical variables as percentage. Comparison between two or

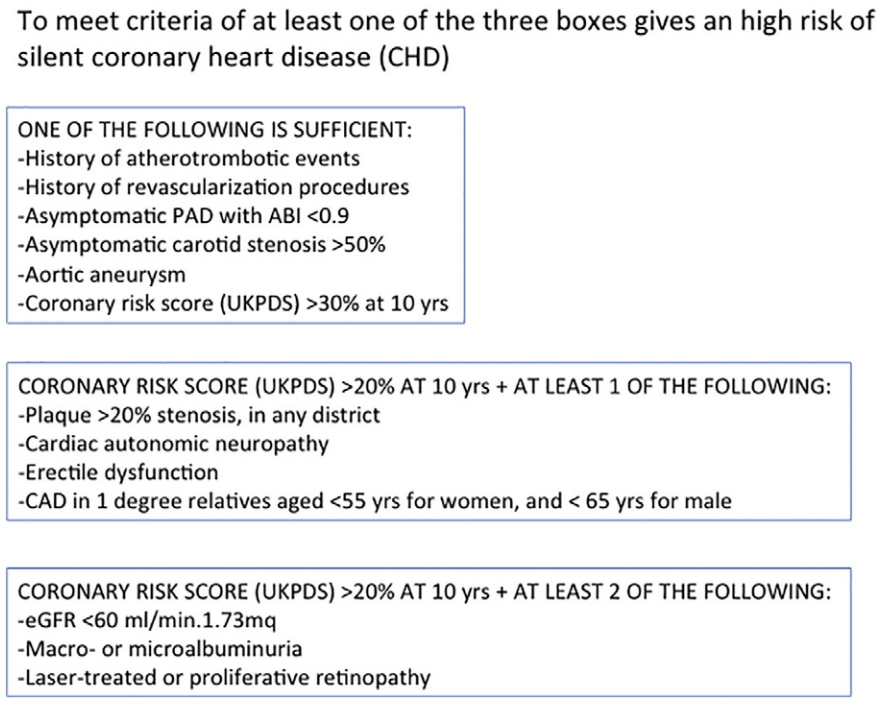

Fig. 1. Definition of the risk of silent myocardial ischemia, as suggested by the Italian Intersociety Consensus.

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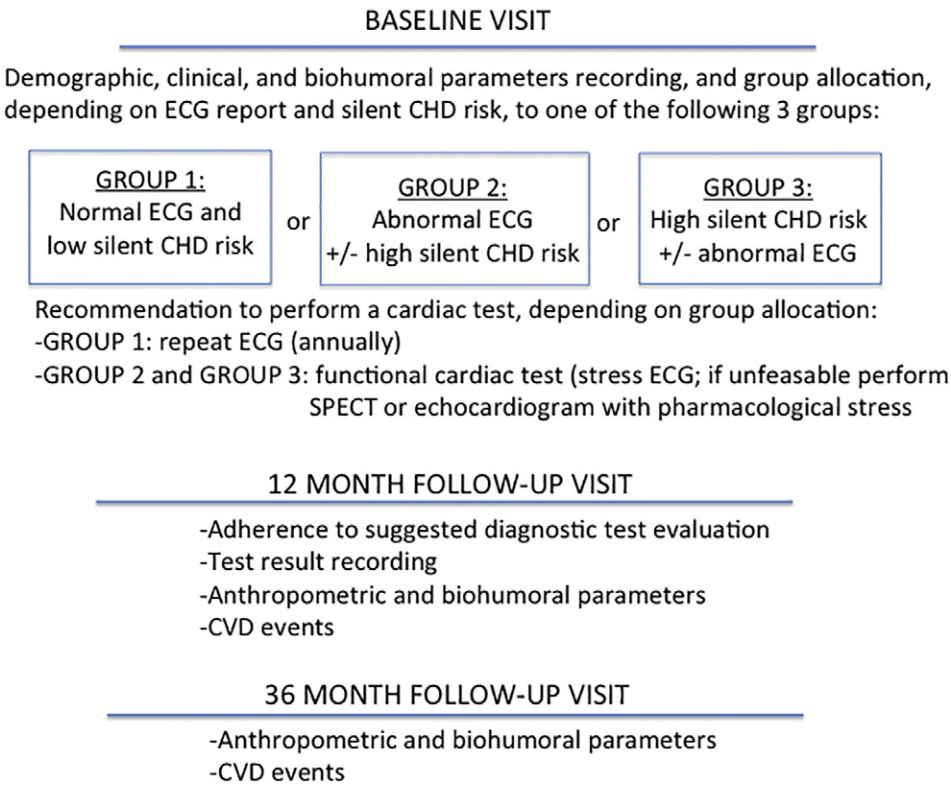

Fig. 2. Study protocol.

more groups was performed with the Student's t test or ANOVA, respectively, for continuous variables with normal distribution, and with Wilcoxon or Kruskal–Wallis test, respectively, for variables with non-normal distribution, and with the chi-square test for categorical data. The least significance difference (LSD) post-hoc test was applied. A multiple logistic regression analysis was applied to identify the variables independently associated with CHD.

Statistical significance was accepted at $p < 0.05$, and SPSS ver. 23 was used.

4. Results

4.1. Baseline study

Main demographic, anamnestic and clinical characteristics of the whole study cohort and comparisons among the 3 predefined groups, at baseline visit, are summarized in Table 1. A different sex distribution was present, among groups; glycated hemoglobin values increased progressively and significantly from group 1 to 3, while HDL cholesterol concentrations progressively lowered; similarly, the prevalence of arterial hypertension, erectile dysfunction, symptomatic peripheral artery disease, and diabetic retinopathy significantly differed among groups, being maximal in the high silent CHD probability subjects.

The most frequent recorded ECG abnormalities were specific alterations of repolarization (n 7), and left axial deviation (n 7). In 4 patients a Q wave was diagnosed, in 4 patients a bundle branch blocks, and in 3 patients negative T waves were found.

4.2. Follow-up at 12 months

At first follow-up visit (12 ± 0.9 months) data were collected on protocol adherence, performed diagnostic test, prevalence of silent CHD diagnosis, and main clinical and biohumoral parameters. Eighty-six patients, out of 102 attended the 12-month follow-up visit. The protocol adherence, the frequency and distribution of performed diagnostic tests, and the screening test results are summarized in Table 2. None of these variable showed statistical differences among groups.

In subjects with positive cardiac functional tests, a coronary angiography (CAG) was performed, to ascertain the presence of significant (>50%) coronary stenosis. In all but 1 case, showing on the other hand a positive echo-stress test, silent CHD was confirmed at CAG. Among subjects showing ECGraphic alterations (group 2), 4 male and 1 female had an ascertained diagnosis of silent CHD, while among subjects with a high pre-test risk of silent CHD (group 3), 4 male had an ascertained diagnosis of silent CHD. Of note, in group 2 only 1 patient showed a high pre-test silent CHD risk, and had a negative functional test. No patient of group 1 (normal ECG) showed clinical or ECG/echocardiographic abnormalities at 12-month follow-up visit.

Interestingly, when we compared subjects with normal (n 70) vs. abnormal (n 32) ECG, the prevalence of CHD was significantly higher in patients with ECG alterations (4% vs. 23%, respectively; $p = 0.004$), whereas, when we compared subjects with a low pre-test silent CHD risk (n 71) and subjects with a high pre-test risk (n 31), a non-significant difference was observed for the prevalence of CHD within groups (9% vs. 14%, respectively; $p = 0.472$).

At this follow-up visit, several anthropometric and biohumoral parameters showed significant improvement, with respect to baseline (Table 3).

Moreover, 2 cardiovascular events were reported: 1 patient of group 1 reported a transitory ischemic attack, and 1 patient of group 2 an episode of heart failure.

4.3. Diagnosis of silent CHD in patients undergone a functional cardiac test

When we restricted the analysis to subjects undergoing a functional cardiac screening test (i.e. group 2 and 3; n 44), among patients with normal (n 16) vs. abnormal (n 28) ECG, the diagnosis of silent CHD was confirmed in 2 patients (12.5%) of the former group, but in 7 patients

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Table 1
Studied variables in the whole cohort, and in predefined subgroups, and comparisons among the 3 subgroups.

Variable	All (n 102)	Group 1 (n 49)	Group 2 (n 23)	Group 3 (n 30)	p
Age (years)	57 ± 7	56 ± 7	58 ± 7	58 ± 6	0.402
Gender (M/F)	55/47	22/27	9/14	24/6**,#	0.002
BMI (kg/m^2)	33 ± 8	34 ± 10	32 ± 6	33 ± 7	0.848
Waist (cm)	111 ± 17	113 ± 21	108 ± 16	109 ± 12	0.637
UKPDS CHD risk	17 ± 10	12 ± 6	15 ± 7	27 ± 10**,#	<0.001
UKPDS fatal CHD risk	10 ± 7	7 ± 5	9 ± 5	17 ± 7**,#	<0.001
UKPDS stroke risk	7 ± 7	6 ± 4	6 ± 4	10 ± 10**,#	0.005
UKPDS fatal stroke risk	1 ± 1	0.8 ± 0.5	0.9 ± 0.6	1.8 ± 1.6**,#	<0.001
DM duration (years)	7 ± 6	6 ± 6	7 ± 6	8 ± 6	0.717
SBP (mmHg)	138 ± 16	134 ± 12	137 ± 15	147 ± 18**,#	0.001
DBP (mmHg)	82 ± 9	82 ± 8	80 ± 11	84 ± 10	0.183
Heart rate (bpm)	78 ± 9	77 ± 8	77 ± 12	80 ± 8	0.268
Glucose (mg/dl)	148 ± 46	137 ± 37	150 ± 59	165 ± 16***	0.032
Glycated haem. (%)	7.7 ± 1.7	7.2 ± 1.5	7.5 ± 1.9	8.6 ± 1.4**,§	0.001
Glycated haem. (Mm)	60 ± 13	55 ± 11	58 ± 15	70 ± 11**,§	0.001
AST (IU/L)	24 ± 11	23 ± 9	23 ± 10	27 ± 15	0.322
ALT (IU/L)	29 ± 20	27 ± 22	29 ± 16	30 ± 21	0.858
Creatinine (mg/dl)	0.92 ± 0.30	0.89 ± 0.27	0.88 ± 0.27	1.00 ± 0.35	0.180
eGFR (ml/min.1.73mq)*	82 ± 20	83 ± 19	82 ± 20	81 ± 23	0.854
AER (median, interquartile range) (mcg/min)	10.00 (4.08–64.60)	7.50 (3.50–15.15)	27.75 (7.70–92.00)	12.00 (2.55–103.95)	0.130
Tot. cholesterol (mg/dl)	197 ± 37	194 ± 34	203 ± 38	197 ± 40	0.365
HDL cholesterol (mg/dl)	48 ± 14	51 ± 14	49 ± 14	41 ± 12**,§	0.003
LDL cholesterol (mg/dl)	119 ± 33	117 ± 31	116 ± 34	119 ± 33	0.453
Triglycerides (mg/dl)	153 ± 103	135 ± 72	158 ± 110	179 ± 133	0.188
Hypertension (%)	80	67	87§	97**	0.004
Dyslipidemia (%)	68	59	82	73	0.127
Hypotensive drugs (%)	75	58	86**	93**	0.001
Hypolipidemic drugs (%)	58	44	74***	70***	0.016
Antiaggregants (%)	29	18	39	40	0.063
Diet (%)	10	11	5	10	0.782
OAD (%)	77	85	77	63	0.080
Metformin (%)	76	83	77	63	0.146
Sulpho. or glinide (%)	21	24	16	20	0.761
Incretins (%)	16	18	16	13	0.879
Glitazone (%)	5	4	16	0	0.053
Insulin (%)	31	19	40	43***	0.050
OAD + Insulin (%)	17	17	16	17	0.993
Retinopathy (%)	17	6	26***	27***	0.022
Nephropathy (%)	16	8	22	23	0.134
Neuropathy (%)	13	8	22	13	0.278
Claudicatio (%)	8	2	4***	21**	0.009
Erectile dysfunction (%)	7	0	6	19**	0.008

DM = diabetes mellitus; SBP = systolic blood pressure; DBP = diastolic blood pressure; AER = albumin excretion rate; OAD = oral antidiabetic drugs; Sulpho. = sulphonilureas. (Group 1: normal ECG, and no high risk of silent CHD; group 2: abnormal ECG, independent of the risk of silent CHD; group 3: high silent CHD risk, independent of ECG or echocardiogram reports.)
Mean ± SD. ANOVA or Kruskal–Wallis test or chi-squared test p-values and post-hoc least significant differences are shown.
* eGFR was calculated with the CKD-EPI method.
** $p < 0.005$ vs. group 1.
*** $p < 0.05$ vs. group 1.
# $p < 0.005$ vs. group 2.
§ $p < 0.05$ vs. group 2.

(25%) of the latter; this comparison however does not reach statistical significance ($p = 0.322$), probably due to the small numbers. Among the 7 patients with abnormal ECG and CHD, 3 showed a low pre-test probability of silent CHD, and 4 a high pre-test probability. On the other hand, both patients with normal ECG and silent CHD showed a high pre-test risk.

When we compared subjects with high silent CHD risk (n 25), calculated as suggested by the Consensus score (Fig. 2), vs. subjects with

Table 2
Adherence to study protocol, performed diagnostic test, and results of silent CHD screening.

	All	Group 1	Group 2	Group 3	p
Subjects (n)	102	49	23	30	
Protocol adherence/enrolled patients (y/n)	80/22 (78%)	36/13 (73%)	20/3 (87%)	24/6 (80%)	0.418
12-mo FU visit (yes/no)	86/16 (84%)	36/13 (73%)	22/1 (96%)	28/2 (93%)	0.147
30-mo FU visit (yes/no)	66/36 (65%)	32/17 (65%)	10/13 (43%)	22/8 (73%)	0.073
Stress-ECG	27/80	0	14	13	–
Echo-stress	9/80	0	2	7	–
MPI	7/80	0	4	3	–
MSCT	1/80	0	0	1	–
Positive test in screened patients (y/n)	10 (14%)	0 (0%)	5/15 (25%)	5/19 (21%)	0.743*
Ascertained silent CHD by CAG	9 (13%)	0 (0%)	5/15 (25%)	4/20 (17%)	0.495*

FU = follow-up. P for ANOVA or *chi-square test between group 2 and 3; MSCT = multi-slice computer tomography.

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Table 3
Comparison of clinical/biohumoral parameters between baseline and 12-month follow-up visits (N 86 subjects).

Variable	Baseline	12 month follow-up	p
Weight (kg)	97 ± 26	92 ± 23	0.015
BMI (kg/m^2)	34 ± 10	33 ± 8	0.025
Waist (cm)	112 ± 18	113 ± 21	0.014
Glucose (mg/dl)	144 ± 44	134 ± 45	0.017
Glycated haem. (%)	7.8 ± 1.8	7.1 ± 1.4	0.002
Glycated haem. (Mm)	62 ± 14	54 ± 11	0.002
AST (IU/L)	24 ± 11	23 ± 12	0.201
ALT (IU/L)	30 ± 21	28 ± 16	0.427
Creatinine (mg/dl)	0.92 ± 0.29	0.89 ± 0.24	0.035
eGFR (ml/min.1.73mq)	82 ± 20	86 ± 19	0.012
AER (Median, interquartile range) (mcg/min)	10.00 (4.08–64.60)	14.00 (2.00–108.00)	0.057
Total cholesterol (mg/dl)	203 ± 36	181 ± 33	<0.001
HDL cholesterol (mg/dl)	47 ± 15	47 ± 15	0.925
LDL cholesterol (mg/dl)	128 ± 32	106 ± 25	<0.001
Triglycerides (mg/dl)	157 ± 93	151 ± 87	0.639

a low pre-test probability (n 19), the prevalence of ascertained silent CHD was not significantly different between groups, though tended to be higher in the low risk group (26% vs. 16%; p = 0.462). Similarly, comparing the patients on the basis of the 10 year UKPDS coronary risk only, i.e. <20% (n 21) or >20% (n 23), the prevalence of silent CHD was alike between groups (19% vs. 22%, respectively; p = 0.825).

These results unravel a stronger association between silent CHD and ECG abnormalities, than between silent CHD and a high disease probability, based on cardiovascular risk factors.

4.4. Follow-up at 36 months

The mean duration of this second follow-up visit was 33 ± 8 months. Sixty-five percent of the whole group attended the follow-up visit 2 (Table 2). Comparing all studied parameters, between the two follow-up visits (12- and 36-months), a statistically significant difference was observed only for LDL-cholesterol, further reduced at the second follow-up visit (104 ± 25 vs. 97 ± 28 mg/dl; p = 0.050). No other significant changes were observed. At this follow-up visit, 3 more cardiovascular events were reported: 2 acute myocardial infarctions and 1 TIA in patients of group 3; it is of note that all these 3 patients showed an abnormal ECG at baseline.

After a mean period of 33 ± 8 months, all patients were alive.

4.5. Event-free survival at final evaluation

A further follow-up visit for vital status and main cardiovascular event occurrence was performed at 56 ± 8 months. Vital status was known for all the subjects; all were alive, but 1 patient of group 3, who died for pulmonary embolism, after a diagnosis of colon cancer. Data on MACE were available for 91 subjects (89%), while it was not possible to collect data on MACE for 11 subjects of the initial cohort, at this final evaluation. One patient of group 3 experienced a TIA, and 2 patients, one of group 2 and one of group 3, experienced an acute coronary syndrome.

Table 4
Logistic regression analysis to estimate the risk of CHD (dependent variable) associated with major CVD-risk variables.

Variables	OR	95% CI	p
Age (years)	1.031	0.894–1.191	0.672
Gender (M/F)	9.541	0.476–191.139	0.140
BMI (kg/m^2)	1.147	0.985–1.336	0.077
UKPDS CHD risk	1.019	0.907–1.145	0.754
ECG abnormalities	8.932	1.275–62.595	0.028
HbA1c (%)	1.094	0.543–2.206	0.801
Dyslipidemia	0.703	0.091–5.465	0.737
Hypertension	0.000	0.000	0.998

For each odds ratio we estimated a two-tailed p values and 95% confidence intervals (CI).

4.6. Logistic regression analysis of variables associated with CHD

Looking for variables independently associated with the diagnosis of CHD, we analyzed by logistic regression the role of ECG abnormalities, UKPDS CHD risk score, hypertension, HbA1c, and dyslipidemia, together with age, gender and BMI. As shown in Table 4, only ECG abnormalities were independently associated with CHD (OR 8.932, 95% CI 1.275–62.595, p < 0.028), further confirming its reliability for the screening of silent myocardial ischemia.

5. Discussion

The usefulness of screening for asymptomatic CHD in diabetic patients has long been debated,[6,11–16] but still remains uncertain. In this study we tested the efficacy of the diagnostic algorithm for silent CHD proposed by the Italian Societies for the Study of Diabetes and Cardiology.[17]

We found that in a cohort of unselected asymptomatic type 2 diabetic subjects, the prevalence of silent CHD is 11%; yet this prevalence almost doubled (20.5%) in patients showing either an abnormal resting ECG or a high pre-test risk of silent CHD. This figure is comparable to that of other studies.[5,7,8] On the other hand, a low risk of silent CHD, determined by CV risk factors, or a normal ECG are unlikely to be associated with silent CHD.

The high probability of silent CHD, as suggested by our Consensus, is based either on the UKPDS Risk Engine, and/or on the presence of micro- and microangiopathy complications, which has been shown to be significantly associated with macrovascular disease.[18,19] Subjects with a high risk score were advised to perform a functional cardiac test, which is also recommended in subjects with an ECG abnormality (apart from the isolated 1st degree atrioventricular block or the incomplete right bundle branch block). We observed a similar prevalence of silent CHD between those with high risk, independent of ECG alterations (group 3), and abnormal ECG, independent of silent CHD risk (group 2). However, when we considered normal vs. abnormal ECG instead of low vs. high pre-test silent CHD risk, the presence of ECG abnormalities seemed to show a better diagnostic performance. To confirm the lesser role of traditional risk factors in identifying diabetic patients at risk of silent CHD, when we compared subjects with vs. without a high UKPDS coronary risk score, the prevalence of ascertained silent CHD between groups was similar.

Conclusively, logistic regression analyses confirmed the independent association of ECG abnormalities with silent CHD.

These findings demonstrate, for the first time in a prospective study, that any ECG alterations should be considered the strongest predictor for silent CHD, while the traditional risk-based approach to identify patients to be screened for silent CHD seems to be of lessened usefulness, as already suggested.[20,21] Moreover in this study, not only ECG alterations suggestive of myocardial infarction were considered for the diagnosis of silent CHD, as in the population of the UKPDS,[5] but whatever ECG abnormality, strengthening the importance of this test in evaluating any diabetic individual. The concept that the manifestation of cardiovascular disease, rather than the disease risk definition should be considered in the single patient, has recently been taken into account and exposed in the 2016 ADA Recommendations. While in the 2015 ADA Position Statement,[22] the screening for CHD was tout-court not recommended, since it failed to improve outcomes, as long as CVD risk factors were treated, in the 2016 recommendations it is suggested "*to consider investigations for coronary artery disease in the presence of … signs or symptoms of associated vascular. disease including carotid bruits, transient ischemic attack, stroke, claudication, or peripheral arterial disease*".[23] This is the first time that overt atherosclerotic disease is suggested as a criterion for silent CHD risk definition, by ADA statements. Also in the Italian intersociety Consensus, the presence of atherosclerosis contributes to the risk definition of silent CHD, but

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compared to this parameter, the presence of specific cardiac alterations, documented at the ECG recording, shows a more important predictive value. Therefore, one relevant observation that we can draw from our results is the importance of performing a standard rest ECG, in all type 2 diabetic patients, every year, as recommended by the Italian Standards of Care for Diabetes.[24]

We found an adherence to the suggested diagnostic protocol in 78% of patients, which is not satisfactory, given that the patients were managed in specialized centers, and informed about their CHD risk. However, another important result of our study is that main metabolic parameters improved significantly at 1-year follow-up visit, in the whole group, although no particular intervention on lifestyle or drug therapy modifications was given. This observation may suggest that the perception of a closer and wider medical supervision positively affects patient behavior, and confirms that better quality of care is guaranteed in dedicated disease centers.[25–27]

Finally, we observed too few cardiovascular events to draw any conclusion about it, being their incidence of about 2% per year, in a follow-up of 56 months. This result is comparable to that observed in the subgroup of the DIAD study cohort defined at high-risk by the UKPDS risk engine (about 2%) .[28] However, all but one were observed in patients with ECG abnormalities, and only 1 event happened in a low risk subjects with normal ECG.

This study has some limitations, mainly residing in the relatively small number of participants and in the incomplete fulfillment of the diagnostic protocol that may reduce the strength of our results; on the other hand the statistical significance obtained in this small cohort reveals the robustness of the findings.

In conclusion, the presence of whatever ECG abnormality, and not only of Q waves or typical ischemic alterations, can be considered a reliable marker of silent myocardial ischemia, in type 2 diabetic subjects.

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